From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 10 July 2000 (10.07.00)	
International application No. PCT/US99/25676	**Applicant's or agent's file reference** 12636-783
International filing date (day/month/year) 01 November 1999 (01.11.99)	**Priority date** (day/month/year) 04 November 1998 (04.11.98)
Applicant WRENN, Simeon, M., Jr.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

31 May 2000 (31.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau f WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Antonia Muller
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PA. ENT COOPERATION TREAT

09/763,497
50C0

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WEITZ, David, J.
Wilson Sonsini Goodrich & Rosati
650 Page Mill Road
Palo Alto, CA 94304-1050
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
28 March 2001 (28.03.01)

Applicant's or agent's file reference
12636-783

IMPORTANT NOTIFICATION

International application No.
PCT/US99/25676

International filing date (day/month/year)
01 November 1999 (01.11.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
SUPERGEN, INC.
Suite 220
Two Annabel Lane
San Ramon, CA 94583
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
SUPERGEN, INC.
Suite 200
4140 Dublin Boulevard
Dublin, CA 94568
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Gen va 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Diana Nissen
Telephone No.: (41-22) 338.83.38

09/763497

15

PATENT COOPERATION TREATY

PCT

REC'D 12 FEB 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
12636-783		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/25676	01/11/1999	04/11/1998
International Patent Classification (IPC) or national classification and IPC A61K9/32		
Applicant SUPERGEN, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31/05/2000	08.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Merkl, B Telephone No. +49 89 2399 2138

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/25676

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-19,22-35	as originally filed	
20,20A,21	with telefax of	31/05/2000

Claims, No.:

1-37	with telefax of	31/05/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☒ the claims, Nos.: 38-46
   - ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 11-37.

because:

   ☒ the said international application, or the said claims Nos. 11-37 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 1-37
Inventive step (IS)	Yes:	Claims

	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Item I:

The subject-matter of claim 1, 11, 24 contravenes Art. 34(2)b PCT as it contains subject-matter extending beyond the content of the application as filed. The combination of 2'-deoxyadenosine analog and a component which inhibits the 2'-deoxyadenosine from decomposing in the acid environment of the stomach by isolating the 2'-deoxyadenosine from the acidic environment of the stomach is not disclosed in the application as filed. No basis for this combination has been submitted.

The subject-matter of claim 2, 12, 25 contravenes Art. 34(2)b PCT as it contains subject-matter extending beyond the content of the application as filed. Pentostatin is disclosed in the application as filed only in connection with a further deoxyadenosin, whereas in claim 2 this restriction is not present. In the examples pentostatin is disclosed only together with specific further features. A generalization which does not take into account said further features creates also subject-matter extending beyond the content of the application as filed.

Item III:

Claims 11-37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Item V:

Claim 1 of the pending application refers to a composition comprising a "2'-deoxyadenosine analog" in combination with an agent protecting said analog from acid decomposition. Any compound disclosed in the prior art which can act as "2'-deoxyadenosine analog" even if not stated explicitly in the prior art has to be taken into account for the evaluation of novelty and inventive step. In such a case it is up to the applicant to submit convincing evidence that a compound disclosed in the prior art does not show the effect of an "2'-deoxyadenosine analog". Compounds which show or which might show said effect are disclosed in the following documents:

D1: WO 98 42352 A (GLAXO GROUP LTD ;AVERETT DEVRON RANDOLPH (US); MCGUIRT PAUL VESTAL) 1 October 1998 (1998-10-01)
D2: EP-A-0 524 579 (SQUIBB BRISTOL MYERS CO) 27 January 1993 (1993-01-27)
D3: WO 90 14091 A (US GOVERNMENT) 29 November 1990 (1990-11-29)
D4: US-A-4 088 756 (VOORHEES JOHN J) 9 May 1978 (1978-05-09)
D5: US-A-5 616 566 (MITSUYA HIROAKI ET AL) 1 April 1997 (1997-04-01)
D6: EP-A-0 068 268 (YAMASA SHOYU KK) 5 January 1983 (1983-01-05)
D7: DATABASE WPI Derwent Publications Ltd., London, GB; AN 1995-032804 XP002133230 'Anti-Aids virus agent microcapsule preparation' & JP 06 316524 A (NAOYUKI INOUE), 15 November 1994 (1994-11-15)
D8: DATABASE WPI Derwent Publications Ltd., London, GB; AN 1983-13049k XP002133231 'Agents for enhancing antitumour effect' & JP 57 209226 A (YAMASA SHOYU KK), 22 December 1982 (1982-12-22)

With respect to D1 it is referred to page 13,lines 23and 24 wherein it is stated that an enteric coating may be provided.

In D2 the use of an antacid compound in order to protect the drug which is not stable in an acid environment is recommended.

In D3 on page 10, lines 5-7 suitable coatings which are resistant to gastric juices are provided.

With respect to D4 it is referred to col. 5, lines 59-64 and col., 6, lines 36-50.

In D5 in col. 4, lines 65-67 it is stated that an enteric coating may be provided for the oral dosage forms. Also the problem that the active agent is not stable in an acid environment has been addressed in D5 (col. 5, lines 28-36).

With respect to D6 it is referred to the examples.

With respect to D7 it should be noted that an ethylcellulose coating is used.

The retard release formulation in D8 implies a certain amount of acid protection.

Further with respect to inventive step it has to be said that the principle to protect drugs which are not stable in acidic environment from decomposition in the stomach, eg by an enteric coating, is known in the art for various kinds of drugs. Therefore the application of said principle to the unstable 2'-deoxyadenosine analog drugs does not imply an inventive step.

Item VII:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1-D7 is not mentioned in the description, nor are these documents identified therein.

Other controlled release technologies that may be used in the practice of this invention are quite varied. They include SODAS, INDAS, IPDAS, MODAS, EFVAS, PRODAS, and DUREDAS. SODAS are multi particulate dosage forms utilizing controlled release beads. INDAS are a family of drug delivery technologies designed to increase the solubility of poorly soluble drugs. IPDAS are multi particulate tablet formation utilizing a combination of high density controlled release beads and an immediate release granulate. MODAS are controlled release single unit dosage forms. Each tablet consists of an inner core surrounded by a semipermeable multiparous membrane that controls the rate of drug release. EFVAS is an effervescent drug absorption system. PRODAS is a family of multi particulate formulations utilizing combinations of immediate release and controlled release mini-tablets. DUREDAS is a bilayer tablet formulation providing dual release rates within the one dosage form. Although these dosage forms are known to one of skill, certain of these dosage forms will now be discussed in more detail.

INDAS was developed specifically to improve the solubility and absorption characteristics of poorly water soluble drugs. Solubility and, in particular, dissolution within the fluids of the gastrointestinal tract is a key factor in determining the overall oral bioavailability of poorly water soluble drug. By enhancing solubility, one can increase the overall bioavailability of a drug with resulting reductions in dosage. INDAS takes the form of a high energy matrix tablet. In a preferred embodiment of the invention production involves including adenosine analogs in an amorphous form together with a combination of energy, excipients, and unique processing procedures.

Once included in the desirable physical form, the resultant high energy complex may be stabilized by an absorption process that utilizes a novel polymer cross-linked technology to prevent recrystallization. The combination of the change in the physical state of the adenosine analogs according to the invention coupled with the solubilizing characteristics of the excipients employed enhances the solubility of the adenosine analogs according to the

invention. The resulting absorbed amorphous drug complex granulate may be formulated with a gel-forming erodable tablet system to promote substantially smooth and continuous absorption.

IPDAS is a multi-particulate tablet technology that may enhance the gastrointestinal tolerability of potential irritant and ulcerogenic drugs. Intestinal protection is facilitated by the multi-particulate nature of the IPDAS formulation which promotes dispersion of an irritant adenosine analog according to the invention throughout the gastrointestinal tract. Controlled release characteristics of the individual beads may avoid high concentration of drug being both released locally and absorbed systemically. The combination of both approaches serves to minimize the potential harm of the adenosine analog according to the invention with resultant benefits to patients.

IPDAS is composed of numerous high density controlled release beads. Each bead may be manufactured by a two step process that involves the initial production of a micromatrix with embedded adenosine analogs according to the invention and the subsequent coating of this micromatrix with polymer solutions that form a rate limiting semipermeable membrane *in vivo*. Once an IPDAS tablet is ingested, it may disintegrate and liberate the beads in the stomach. These beads may subsequently pass into the duodenum and along the gastrointestinal tract, preferably in a controlled and gradual manner, independent of the feeding state. Adenosine analog release occurs by diffusion process through the micromatrix and subsequently through the pores in the rate controlling semipermeable membrane. The release rate from the IPDAS tablet may be customized to deliver a drug-specific absorption profile associated with optimized clinical benefit. Should a fast onset of activity be necessary, immediate release granulate may be included in the tablet. The tablet may be broken prior to administration, without substantially compromising drug release, if a reduced dose is required for individual titration.

MODAS is a drug delivery system that may be used to control the absorption of water soluble adenosine analogs according to the invention.

WHAT IS CLAIMED IS:

1. A composition comprising an adenosine analog, wherein the composition comprises a dosage form suitable for oral (co)administration.

2. The composition of claim 1, wherein the composition comprises a controlled release composition.

3. The composition of claim 1, wherein the composition comprises a dosage form that reduces acid lability of the adenosine analog, thereby enhancing bioavailability of the adenosine analog.

4. The composition of claim 3, wherein the composition comprises a controlled release composition.

5. The composition of claim 4, wherein the composition is in a dosage form that comprises a physical system or a chemical system.

6. The composition of claim 5, wherein the physical system comprises reservoir systems with rate-controlling membranes; reservoir systems without rate-controlling membranes; monolithic systems; materials physically dispersed in non-porous, polymeric, or elastomeric matrices; laminated structures; osmotic pumps; or adsorption onto ion-exchange resins.

7. The composition of claim 5, wherein the chemical system comprises polymer matrices that are erodible chemically or biologically.

8. The composition of claim 4, wherein the composition comprises a rate-preprogrammed drug delivery system, an activation-modulated drug

delivery system, a feedback-regulated drug delivery system, or a site-targeting drug delivery system.

9. The composition of claim 4, wherein the composition is in a dosage form comprising SODAS, INDAS, IPDAS, MODAS, EFVAS, PRODAS, or DUREDAS.

10. The composition of claim 4, wherein the composition is in a dosage form suitable for delivery orally, mucosally, or nasally.

11. The composition of claim 4, wherein the composition comprises an enteric coating.

12. The composition of claim 11, wherein the enteric coating comprises hydroxypropyl-methylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate.

13. The composition of claim 4, wherein the composition comprises a solid dispersion.

14. The composition of claim 13, wherein the solid dispersion comprises a water soluble or a water insoluble carrier.

15. The composition of claim 14, wherein the water soluble or water insoluble carrier comprises polyethylene glycol, polyvinylpyrrolidone, hydroxypropylmethyl - cellulose, phosphatidylcholine, polyoxyethylene hydrogenated castor oil, hydroxypropylmethylcellulose phthalate, carboxymethylethylcellulose, or hydroxypropylmethylcellulose, ethyl cellulose, or stearic acid

16. The composition of claim 4, wherein the composition is in a dosage form comprising a complex between an ion exchange resin and the adenosine analog.

17. The composition of claim 4, wherein the composition is in a dosage form comprising injectable micro spheres.

18. The composition of claim 1, wherein the composition is in a dosage form comprising a pill, capsule, liquid, lozenge, or tablet.

19. The composition of claim 1, wherein liquid dosage forms, controlled release dosage forms, or liposomal dosage forms are excluded.

20. The composition of claim 19, wherein the excluded controlled release dosage forms comprise a physical system or a chemical system.

21. The composition of claim 20, wherein the physical system comprises reservoir systems with rate-controlling membranes; reservoir systems without rate-controlling membranes; monolithic systems; materials physically dispersed in non-porous, polymeric, or elastomeric matrices; laminated structures; osmotic pumps; or adsorption onto ion-exchange resins.

22. The composition of claim 20, wherein the chemical system comprises polymer matrices that are erodible chemically or biologically.

23. The composition of claim 19, wherein the excluded controlled release dosage forms comprise a rate-preprogrammed drug delivery system, an activation-modulated drug delivery system, a feedback-regulated drug delivery system, or a site-targeting drug delivery system.

24. The composition of claim 19, wherein the excluded controlled release dosage forms comprise an enteric coating.

25. The composition of claim 19, wherein the excluded controlled release dosage forms comprise a solid dispersion.

26. The composition of claim 25, wherein the solid dispersion comprises a water soluble or a water insoluble carrier.

27. The composition of claim 1, wherein the adenosine analog is present in an amount effective to treat hematological malignancies, solid tumors sensitive to adenosine analogs or adenosine deaminase inhibitors, ischemia, CD4+ T cell mediated diseases, autoimmune diseases mediated by adenosine or adenosine deaminase, inflammatory diseases mediated by adenosine or adenosine deaminase, stroke, myocardial infarction, and ventricular arrhythmia.

28. The composition of claim 1, wherein the adenosine analog is present in an amount effective to treat a leukemia.

29. The composition of claim 28, wherein the leukemia comprises hairy cell leukemia, and chronic lymphocytic leukemia, chronic T-cell lymphoma, acute myelogenous lymphoma, hairy cell leukemia, or chronic lymphocytic leukemia.

30. A composition comprising adenosine analogs, wherein the composition is in a dosage form comprising a pill, capsule, lozenge, or tablet.

31. A composition comprising adenosine analogs, wherein the composition is in a dosage form comprising a liquid.

32. Methods of administering compositions comprising adenosine analogs to a host in need thereof, comprising:

providing the composition of claim 1, and

administering the composition to the host.

33. The method of claim 32, wherein the composition comprises a controlled release composition.

34. The method of claim 32, wherein the composition comprises a dosage form that reduces acid lability of the adenosine analog, thereby enhancing bioavailability the adenosine analog.

35. The method of claim 34, wherein the composition comprises a controlled release composition.

36. The method of claim 32, wherein the composition is in a dosage form that comprises a physical system or a chemical system.

37. The method of claim 36, wherein the physical system comprises reservoir systems with rate-controlling membranes; reservoir systems without rate-controlling membranes; monolithic systems; materials physically dispersed in non-porous, polymeric, or elastomeric matrices; laminated structures; osmotic pumps; or adsorption onto ion-exchange resins.

38. The method of claim 32, wherein the composition comprises a rate-preprogrammed drug delivery system, an activation-modulated drug delivery system, a feedback-regulated drug delivery system, or a site-targeting drug delivery system.

39. The method of claim 32, wherein the composition is in a dosage form comprising SODAS, INDAS, IPDAS, MODAS, EFVAS, PRODAS, or DUREDAS.

40. The method of claim 32, wherein the composition is in a dosage form suitable for delivery orally, mucosally, or nasally.

41. The method of claim 32, wherein the composition comprises an enteric coating.

42. The method of claim 32, wherein the composition comprises a solid dispersion.

43. The method of claim 42, wherein the solid dispersion comprises a water soluble or a water insoluble carrier.

44. The method of claim 32, wherein the composition is in a dosage form comprising a complex between an ion exchange resin and the adenosine analog.

45. The method of claim 32, wherein the composition is in a dosage form comprising injectable micro spheres.

46. A kit comprising the composition of claim 1.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 12636-783

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US99/25676	01 November 1999 (01.11.99)	04 November 1998 (04.11.98)

Title of invention: ORAL ADMINISTRATION OF ADENOSINE ANALOGS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SUPERGEN, INC.
Two Annabel Lane, Suite 220
San Ramon, CA 94583
US

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WRENN, Simeon M., Jr
120 Montair Court
Danville, California 94526
US

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US99/25676

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

And ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier..

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

David J. WEITZ
WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, California 94304-1050
US

Telephone No.: (650) 493-9300
Facsimile No.: (650) 493-6811
Teleprinter No.:

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☐ the international application as originally filed

the description ☐ as originally filed
☒ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☒ as amended under Article 34

the drawings ☒ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 6.91(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

NO EXCEPTIONS

See Notes to the demand form

International application No.
PCT/US99/25676

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:				For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:		sheets	☐	☐
2. amendments under Article 34	:	17	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:		sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:		sheets	☐	☐
5. letter	:		sheets	☐	☐
6. other *(specify)*	:		sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ nucleotide and or amino acid sequence listing in computer readable form
6. ☒ other *(specify)* transmittal and postcard

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

David J. Weitz

David J. WEITZ

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

See Notes to the demand form

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No.	PCT/US99/25676
Applicant's or agent's file reference	12636-783

For International Preliminary Examining Authority use only

Date stamp of the IPEA

Applicant

SUPERGEN, INC.

Calculation of prescribed fees

1. Preliminary examination fee	1,533 EUR	P
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	147 EUR	H
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David J. Weitz
Signature: David J. Weitz,
Reg. No. 38,362 (12636-783)

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Signature: David J. Weitz
David J. Weitz, Reg. No. 38,362 (12636-783)

Place, Date: Palo ALto. California U.S.A. 31 May 2000

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Atty. Docket: 12636-783

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
IN THE EUROPEAN PATENT OFFICE

In re Application	)	PCT PATENT APPLICATION
SuperGen, Inc.	)	
Application No.: PCT/US99/25676	)	
Filed: 01 November, 1999	)	
Title: Oral Administration of Adenosine Analogs	)	
	)	

AMENDMENT UNDER ARTICLE 34

European Patent Office
Erhardstrasse 27
D-80298 Munchen 2
Germany

Applicant files herewith a Chapter II Demand requesting International Preliminary Examination. The Applicant requests that the following Amendments to the claims be taken into account for purposes of International Preliminary Examination.

AMENDMENTS

Applicants amend the above identified PCT patent application as follows:

In the Specification:

Please amend the Specification as follows:

At Page 20, Line 2, delete:

"They include SODAS, INDAS, IPDAS, MODAS, EFVAS, PRODAS, and DUREDAS."

And insert:

--They include SODAS (Spheroidal Oral Drug Absorption System), INDAS (Insoluble Drug Absorption System), IPDAS (Intestinal Protective Drug Absorption System), MODAS (Multiple Oral Drug Absorption System), EFVAS (Effervescent Drug Absorption System), PRODAS (Programmable Oral Drug Absorption System), and DUREDAS (Dual Release Drug Absorption System) available from Elan Pharmaceutical Technologies, Dublin, Ireland.--

In the Claims

Please cancel claims 1-46.

Please add new claims 47-83:

47. A composition comprising:

2'-deoxyadenosine analog which chemically decomposes in an acidic environment of the stomach; and

one or more components which inhibit the 2'-deoxyadenosine analog from decomposing in the acidic environment of the stomach by isolating the 2'-deoxyadenosine analog from the acidic environment of the stomach;

wherein the composition is suitable to be administered orally to a patient.

48. The composition according to claim 47 wherein the 2'-deoxyadenosine analog is pentostatin.

49. The composition according to claim 47 wherein the one or more components of the composition form an erodible matrix.

50. The composition according to claim 47 wherein the one or more components of the composition include an enteric coating.

51. The composition according to claim 50 wherein the enteric coating comprises a member of the group consisting of hydroxypropyl-methylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate.

52. The composition according to claim 47 wherein the composition is a solid dispersion.

53. The composition according to claim 52 wherein the solid dispersion comprises a carrier selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, hydroxypropylmethyl-cellulose, phosphatidylcholine, polyoxyethylene hydrogenated castor oil, hydroxypropylmethylcellulose phthalate, carboxymethylethylcellulose, hydroxypropylmethylcellulose, ethyl cellulose and stearic acid.

54. The composition according to claim 47 wherein the one or more components of the composition include an ion exchange resin that forms a complex with the adenosine analog.

55. The composition according to claim 47 wherein the one or more components of the composition include injectable micro spheres.

56. The composition according to claim 47 wherein the composition is in a form selected from the group consisting of pill, capsule, liquid, lozenge, and tablet.

57. A method for treating a patient comprising:

orally administering to the patient a pharmaceutically-effective amount of a composition which is adapted for oral administration and comprises:

a 2'-deoxyadenosine analog which chemically decomposes in an acidic environment of the stomach, and

one or more components of the composition which inhibit the 2'-deoxy adenosine analog from decomposing in the acidic environment of the stomach by isolating the adenosine analog from the acidic environment of the stomach.

58. The method according to claim 57 wherein the 2'-deoxyadenosine analog is pentostatin.

59. The method according to claim 57 wherein the one or more components of the composition form an erodible matrix.

60. The method according to claim 57 wherein the one or more components of the composition include an enteric coating.

61. The method according to claim 60 wherein the enteric coating comprises a member of the group consisting of hydroxypropyl-methylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate.

62. The method according to claim 57 wherein the composition is a solid dispersion.

63. The method according to claim 62 wherein the solid dispersion comprises a carrier selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, hydroxypropylmethyl - cellulose, phosphatidylcholine, polyoxyethylene hydrogenated castor oil, hydroxypropylmethylcellulose phthalate, carboxymethylethylcellulose, hydroxypropylmethylcellulose, ethyl cellulose and stearic acid.

64. The method according to claim 57 wherein the one or more components of the composition comprise an ion exchange resin that forms a complex with the adenosine analog.

65. The method according to claim 57 wherein the one or more components of the composition comprise injectable micro spheres.

66. The method according to claim 57 wherein the composition is in a form selected from the group consisting of pill, capsule, liquid, lozenge, and tablet.

67. The method according to claim 57 wherein the patient has a disease selected from the group consisting of hematological malignancies, solid tumors sensitive to adenosine analogs or adenosine deaminase inhibitors, and autoimmune diseases mediated by adenosine or adenosine deaminase.

68. The method according to claim 57 wherein the patient has leukemia.

69. The method according to claim 57 wherein the patient has a leukemia selected from the group consisting of hairy cell leukemia, and chronic lymphocytic leukemia, chronic T-cell lymphoma, acute myelogenous lymphoma, hairy cell leukemia, and chronic lymphocytic leukemia.

70. A method for treating a patient comprising:

orally administering in a controlled-release mechanism to the patient a composition which is adapted for oral administration and comprises:

a 2'-deoxyadenosine analog which chemically decomposes in an acidic environment of the stomach, and

one or more components of the composition which inhibit the 2'-deoxyadenosine analog from decomposing in the acidic environment of the stomach by isolating the 2'-deoxyadenosine analog from the acidic environment of the stomach.

71. The method according to claim 70 wherein the 2'-deoxy adenosine analog is pentostatin.

72. The method according to claim 70 wherein the controlled-release mechanism is selected from the group consisting of a reservoir system with a rate-controlling membrane, reservoir system without a rate-controlling membrane, monolithic system, and osmotic pump.

73. The method according to claim 70 wherein the controlled-release mechanism is selected from the group consisting of SODAS, INDAS, IPDAS, MODAS, EFVAS, PRODAS, and DUREDAS.

74. The method according to claim 70 wherein the one or more components of the composition form an erodible matrix.

75. The method according to claim 70 wherein the controlled-release mechanism is selected from the group consisting of a rate-preprogrammed drug delivery system, an activation-modulated drug delivery system, a feedback-regulated drug delivery system, and a site-targeting drug delivery system.

76. The method according to claim 70 wherein the composition includes an enteric coating.

77. The method according to claim 76 wherein the enteric coating comprises a member of the group consisting of hydroxypropyl-methylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate.

78. The method according to claim 70 wherein the one or more components of the composition include an ion exchange resin that forms a complex with the 2'-deoxyadenosine analog.

79. The method according to claim 70 wherein the one or more components of the composition include injectable micro spheres.

80. The method according to claim 70 wherein the composition is in a form selected from the group consisting of pill, capsule, liquid, lozenge, and tablet.

81. The method according to claim 70 wherein the patient has a disease selected from the group consisting of hematological malignancies, solid tumors sensitive to adenosine analogs or adenosine deaminase inhibitors, and autoimmune diseases mediated by adenosine or adenosine deaminase.

82. The method according to claim 70 wherein the patient has leukemia.

83. A method according to claim 82 wherein the patient has a leukemia selected from the group consisting of hairy cell leukemia, and chronic lymphocytic leukemia, chronic T-cell lymphoma, acute myelogenous lymphoma, hairy cell leukemia, and chronic lymphocytic leukemia.

CONCLUSION

Claims 1-46 have been cancelled. Claims 47-83 have been added. Applicant states that no new matter has been introduced with regard to the above amendments, and respectfully requests that the amendments be taken into account during the international preliminary examination. Substitute pages 20, 20A, 21, 36-41 are presented herewith showing the amendments.

Respectfully submitted,

Date: 31 May 2000 By: David J. Weitz

David J. Weitz, Reg. No. 38,362

WILSON, SONSINI, GOODRICH & ROSATI

650 Page Mill Road

Palo Alto, California 94304-1050

Telephone: (650) 493-9300

Other controlled release technologies that may be used in the practice of this invention are quite varied. They include SODAS (Spheroidal Oral Drug Absorption System), INDAS (Insoluble Drug Absorption System), IPDAS (Intestinal Protective Drug Absorption System), MODAS (Multiple Oral Drug Absurption System), EFVAS (Effervescent Drug Absorption System), PRODAS (Programmable Oral Drug Absorption System), and DUREDAS (Dual Release Drug Absorption System) available from Elan Pharmaceutical Technologies, Dublin, Ireland . SODAS are multi particulate dosage forms utilizing controlled release beads. INDAS are a family of drug delivery technologies designed to increase the solubility of poorly soluble drugs. IPDAS are multi particulate tablet formation utilizing a combination of high density controlled release beads and an immediate release granulate. MODAS are controlled release single unit dosage forms. Each tablet consists of an inner core surrounded by a semipermeable multiparous membrane that controls the rate of drug release. EFVAS is an effervescent drug absorption system. PRODAS is a family of multi particulate formulations utilizing combinations of immediate release and controlled release mini-tablets. DUREDAS is a bilayer tablet formulation providing dual release rates within the one dosage form. Although these dosage forms are known to one of skill, certain of these dosage forms will now be discussed in more detail.

INDAS was developed specifically to improve the solubility and absorption characteristics of poorly water soluble drugs. Solubility and, in particular, dissolution within the fluids of the gastrointestinal tract is a key factor in determining the overall oral bioavailability of poorly water soluble drug. By enhancing solubility, one can increase the overall bioavailability of a drug with resulting reductions in dosage. INDAS takes the form of a high energy matrix tablet. In a preferred embodiment of the invention production involves including adenosine analogs in an amorphous form together with a combination of energy, excipients, and unique processing procedures.

Once included in the desirable physical form, the resultant high energy complex may be stabilized by an absorption process that utilizes a novel

invention coupled with the solubilizing characteristics of the excipients employed enhances the solubility of the adenosine analogs according to the invention. The resulting absorbed amorphous drug complex granulate may be formulated with a gel-forming erodable tablet system to promote substantially smooth and continuous absorption.

IPDAS is a multi-particulate tablet technology that may enhance the gastrointestinal tolerability of potential irritant and ulcerogenic drugs. Intestinal protection is facilitated by the multi-particulate nature of the IPDAS formulation which promotes dispersion of an irritant adenosine analog according to the invention throughout the gastrointestinal tract. Controlled release characteristics of the individual beads may avoid high concentration of drug being both released locally and absorbed systemically. The combination of both approaches serves to minimize the potential harm of the adenosine analog according to the invention with resultant benefits to patients.

IPDAS is composed of numerous high density controlled release beads. Each bead may be manufactured by a two step process that involves the initial production of a micromatrix with embedded adenosine analogs according to the invention and the subsequent coating of this micromatrix with polymer solutions that form a rate limiting semipermeable membrane *in vivo*. Once an IPDAS tablet is ingested, it may disintegrate and liberate the beads in the stomach. These beads may subsequently pass into the duodenum and along the gastrointestinal tract, preferably in a controlled and gradual manner, independent of the feeding state. Adenosine analog release occurs by diffusion process through the micromatrix and subsequently through the pores in the rate controlling semipermeable membrane. The release rate from the IPDAS tablet may be customized to deliver a drug-specific absorption profile associated with optimized clinical benefit. Should a fast onset of activity be necessary, immediate release granulate may be included in the tablet. The tablet may be broken prior to administration, without substantially compromising drug release, if a reduced dose is required for individual titration.

MODAS is a drug delivery system that may be used to control the absorption of water soluble adenosine analogs according to the invention.

WHAT IS CLAIMED IS:

1. A composition comprising:

2'-deoxyadenosine analog which chemically decomposes in an acidic environment of the stomach; and

one or more components which inhibit the 2'-deoxyadenosine analog from decomposing in the acidic environment of the stomach by isolating the 2'-deoxyadenosine analog from the acidic environment of the stomach;

wherein the composition is suitable to be administered orally to a patient.

2. The composition according to claim 1 wherein the 2'-deoxyadenosine analog is pentostatin.

3. The composition according to claim 1 wherein the one or more components of the composition form an erodible matrix.

4. The composition according to claim 1 wherein the one or more components of the composition include an enteric coating.

5. The composition according to claim 4 wherein the enteric coating comprises a member of the group consisting of hydroxypropyl-methylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate.

6. The composition according to claim 1 wherein the composition is a solid dispersion.

7. The composition according to claim 6 wherein the solid dispersion comprises a carrier selected from the group consisting of

polyethylene glycol, polyvinylpyrrolidone, hydroxypropylmethyl-cellulose, phosphatidylcholine, polyoxyethylene hydrogenated castor oil, hydroxypropylmethylcellulose phthalate, carboxymethylethylcellulose, hydroxypropylmethylcellulose, ethyl cellulose and stearic acid.

8. The composition according to claim 1 wherein the one or more components of the composition include an ion exchange resin that forms a complex with the adenosine analog.

9. The composition according to claim 1 wherein the one or more components of the composition include injectable micro spheres.

10. The composition according to claim 1 wherein the composition is in a form selected from the group consisting of pill, capsule, liquid, lozenge, and tablet.

11. A method for treating a patient comprising:

orally administering to the patient a pharmaceutically-effective amount of a composition which is adapted for oral administration and comprises:

a 2'-deoxyadenosine analog which chemically decomposes in an acidic environment of the stomach, and

one or more components of the composition which inhibit the 2'-deoxy adenosine analog from decomposing in the acidic environment of the stomach by isolating the adenosine analog from the acidic environment of the stomach.

12. The method according to claim 11 wherein the 2'-deoxyadenosine analog is pentostatin.

13. The method according to claim 11 wherein the one or more components of the composition form an erodible matrix.

14. The method according to claim 11 wherein the one or more components of the composition include an enteric coating.

15. The method according to claim 14 wherein the enteric coating comprises a member of the group consisting of hydroxypropyl-methylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate.

16. The method according to claim 11 wherein the composition is a solid dispersion.

17. The method according to claim 16 wherein the solid dispersion comprises a carrier selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, hydroxypropylmethyl - cellulose, phosphatidylcholine, polyoxyethylene hydrogenated castor oil, hydroxypropylmethylcellulose phthalate, carboxymethylethylcellulose, hydroxypropylmethylcellulose, ethyl cellulose and stearic acid.

18. The method according to claim 11 wherein the one or more components of the composition comprise an ion exchange resin that forms a complex with the adenosine analog.

19. The method according to claim 11 wherein the one or more components of the composition comprise injectable micro spheres.

20. The method according to claim 11 wherein the composition is in a form selected from the group consisting of pill, capsule, liquid, lozenge, and tablet.

21. The method according to claim 11 wherein the patient has a disease selected from the group consisting of hematological malignancies, solid tumors sensitive to adenosine analogs or adenosine deaminase inhibitors, and autoimmune diseases mediated by adenosine or adenosine deaminase.

22. The method according to claim 11 wherein the patient has leukemia.

23. The method according to claim 11 wherein the patient has a leukemia selected from the group consisting of hairy cell leukemia, and chronic lymphocytic leukemia, chronic T-cell lymphoma, acute myelogenous lymphoma, hairy cell leukemia, and chronic lymphocytic leukemia.

24. A method for treating a patient comprising:

orally administering in a controlled-release mechanism to the patient a composition which is adapted for oral administration and comprises:

a 2'-deoxyadenosine analog which chemically decomposes in an acidic environment of the stomach, and

one or more components of the composition which inhibit the 2'-deoxyadenosine analog from decomposing in the acidic environment of the stomach by isolating the 2'-deoxyadenosine analog from the acidic environment of the stomach.

25. The method according to claim 24 wherein the 2'-deoxy adenosine analog is pentostatin.

26. The method according to claim 24 wherein the controlled-release mechanism is selected from the group consisting of a reservoir system with a rate-controlling membrane, reservoir system without a rate-controlling membrane, monolithic system, and osmotic pump.

27. The method according to claim 24 wherein the controlled-release mechanism is selected from the group consisting of SODAS, INDAS, IPDAS, MODAS, EFVAS, PRODAS, and DUREDAS.

28. The method according to claim 24 wherein the one or more components of the composition form an erodible matrix.

29. The method according to claim 24 wherein the controlled-release mechanism is selected from the group consisting of a rate-preprogrammed drug delivery system, an activation-modulated drug delivery system, a feedback-regulated drug delivery system, and a site-targeting drug delivery system.

30. The method according to claim 24 wherein the composition includes an enteric coating.

31. The method according to claim 30 wherein the enteric coating comprises a member of the group consisting of hydroxypropyl-methylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate.

32. The method according to claim 24 wherein the one or more components of the composition include an ion exchange resin that forms a complex with the 2'-deoxyadenosine analog.

33. The method according to claim 24 wherein the one or more components of the composition include injectable micro spheres.

34. The method according to claim 24 wherein the composition is in a form selected from the group consisting of pill, capsule, liquid, lozenge, and tablet.

35. The method according to claim 24 wherein the patient has a disease selected from the group consisting of hematological malignancies, solid tumors sensitive to adenosine analogs or adenosine deaminase inhibitors, and autoimmune diseases mediated by adenosine or adenosine deaminase.

36. The method according to claim 24 wherein the patient has leukemia.

37. A method according to claim 36 wherein the patient has a leukemia selected from the group consisting of hairy cell leukemia, and chronic lymphocytic leukemia, chronic T-cell lymphoma, acute myelogenous lymphoma, hairy cell leukemia, and chronic lymphocytic leukemia.

5